Allergology International (1999) 48: 69–78

Original Article

A longitudinal observation of sensitization to Japanese cedar pollen and house dust mite among schoolchildren

Kotaro Ozasa,[1] Kenji Dejima,[2] Yoshiyuki Watanabe[3] and Hiroshi Takenaka[4]

Departments of [1]Preventive Medicine and [2]Otorhinopharyngolaryngology, Kyoto Prefectural University of Medicine, [3]Department of Social Medicine and Cultural Sciences, Research Institute for Neurological Diseases and Geriatrics, Kyoto Prefectural University of Medicine, Kyoto and [4]Department of Otorhinopharyngolaryngology, Osaka Medical College, Takatsuki, Osaka, Japan

Abstract

The objective of this study was to identify the risk factors for sensitization to Japanese cedar pollen (JCP) and house dust mite (HDM). The purpose was to clarify how children become sensitized to JCP and HDM and to evaluate the risk factors for sensitization to those antigens. A cohort of 267 children aged 6–11 years was surveyed using a self-administered questionnaire for symptoms and environmental factors such as passive smoking and the condition of the subject's home in 1994. A serum examination of JCP- and HDM-immunoglobulin E was also conducted every year from 1994 to 1997. A total of 35% of the children were positive to JCP in the first survey and a further 19% were positive in at least one of the subsequent three annual surveys. Twenty-seven percent of the children were sensitized to HDM in the first survey and a further 12% were sensitized in at least one of the subsequent three annual surveys. The incidence of JCP sensitization in any one year was proportional to the pollen count. No other environmental factors could be associated with the prevalence of either sensitization or the incidence of JCP sensitization, but HDM sensitization was more common in less well-ventilated houses (relative risk (RR) = 3.42, 95% confidence interval (CI) = 1.03–11.38) and among those who use kerosene stoves (RR = 3.42, 95% CI = 1.26–9.23). The susceptibility to an antigen varies continuously and cannot be divided in a dichotomous manner. The children who had already been sensitized when they were enrolled in this study were of such strong susceptibility to the antigen that they could be sensitized by the minimum exposure to the antigen regardless of the environmental factors. Those with weak susceptibility could be sensitized by an extraordinarily high exposure to the antigen or by environmental risk factors during school age.

Key words: allergy, epidemiology, hay fever, house dust mite, Japanese cedar, longitudinal observation, sensitization.

Introduction

Sensitization to a specific antigen is thought to be regulated by individual susceptibility, exposure to the antigen and non-specific environmental factors. It is also thought that susceptibility is determined by genetic disposition and other individual characteristics.[1] Many studies have shown that the prevalence of allergic disease and sensitization to a specific allergen have been increasing recently.[1] Further, some repeated observations showed that the prevalence of being positive to antigen-specific immunoglobulin E (IgE) has increased.[2–4] The association between environmental factors and allergic diseases has been shown in cross-sectional studies, which may be biased because the prevalent sufferers of an allergic disease may have already changed their lifestyle because of their disease. A study using incident cases of sensitization to a specific allergen is necessary to clarify how people are sensitized to allergens by the interaction between the individual susceptibility, exposure to the allergen, and environmental factors.

Correspondence: Kotaro Ozasa, Department of Preventive Medicine, Kyoto Prefectural University of Medicine, Kyoto, 602–8566, Japan. Email: kozasa@basic.kpu-m.ac.jp

Received 13 July 1998. Accepted for publication 22 September 1998.

Japanese cedar pollinosis (JCPS) is the most common hay fever in Japan in spring. It was first reported in 1964 by Horiguchi and Saito, and has markedly increased since then.[5] People are thought to be sensitized to Japanese cedar pollen (JCP) at a young age, but the natural course of sensitization to it has not yet been clarified. Mori reported in a cross-sectional study that the critical age for sensitization to JCP was 7 years.[6] A longitudinal study showed that the prevalence of being positive to JCP-IgE had increased with time, but that an association between exposure to the antigen and prevalence was not studied.[3] Some studies of ecological, cross-sectional, and case-control design have also analyzed environmental factors.[7–12]

The house dust mite (HDM) is a common indoor allergen and poorly ventilated housing is thought to cause sensitization to HDM.[1] The prevalence of sensitivity to HDM-IgE has also increased in Japan.[3] The environmental factors associated with HDM sensitivity have also been analyzed using prevalent cases sensitized to HDM in Japan.[13,14]

The purpose of this study is to clarify how children become sensitized to JCP and HDM. We have already reported that older children have a high prevalence of being positive to JCP- and HDM-IgE,[12] suggesting that the incident cases of sensitization to JCP and HDM can be identified by a longitudinal observation of children of school age. Therefore, the level of JCP- and HDM-IgE of a defined group of schoolchildren in an area was observed for 4 years.

Attention should be paid to the different characteristics of JCP and HDM. Japanese cedar pollen is an outdoor allergen which is widely dispersed in any one area and thus the strength of the exposure to it can be assumed equal among children in a school for a specific spring season, although it varies widely year by year. However, HDM is a common indoor allergen and the strength of the exposure to it is hardly expected to change for a specific person unless the condition of his or her house changes, but it varies from person to person. It is useful to analyze the allergens with these different characteristics by comparing them in the same subjects.

Materials and methods

The study base comprised all 405 children of a primary school in a rural town in 1994. The population of the town was around 6200 and it is located in a hilly region of southern Kyoto Prefecture. There is only one primary school and junior high school in the town, and hardly any children go to other schools outside the town. Thus, most of the graduates from the primary school go to the junior high school. The survey, which consisted of a questionnaire and serum examination of IgE, was conducted in the years 1994–97. At the initial survey in 1994, 397 children were examined. In total, 267 children participated in all of the serum examinations in 1994–97, and they were the subjects for this current study. This study group consisted of 139 males and 128 females, with 44, 44, 41, 48, 49 and 41 of these children being aged 6, 7, 8, 9, 10 and 11 years in April 1994, respectively.

Dispersed pollen was observed on the roof of the second floor of a building from 1 February to 30 April every year in order to evaluate the exposure to the antigen. The building is near the two schools and they are located almost in the center of the town, which is situated in a small basin. A Vaseline-coated slide glass was set outside (in the shade protected from rain) for 24 h using a Durham sampler. Pollen grains which had naturally fallen on it were counted. The measurement is presented as number of pollen per square centimeter on the glass.[7] The amount of pollen from both Japanese cedar and Japanese cypress was recorded because they have strong cross-antigenicity. The measurement in a certain year is presented as the summation of the count from 1 February to 30 April.

Nasal and/or conjunctival symptoms were surveyed by a self-administered questionnaire which was answered by a parent of each subject. It was carried out in May of each year. Students were asked: 'Did you have any of the following symptoms this March or April?', the following symptoms being sneezing, nasal discharge, nasal obstruction, itching of nasal mucosa, itching of conjunctiva, watering eyes, or eye irritation as caused by foreign matter. Students were also asked 'How long did the symptom(s) last?' The answer was chosen out of: less than one week, 1–3 weeks, 3–4 weeks, or more than 4 weeks. In the first question in 1994, the words 'in March or April in an average year' were used instead of the words 'this March or April'.

Japanese cedar pollen and HDM-IgE were examined just after the questionnaire survey every year and measured by Pharmacia CAP System at SRL Inc. (Tokyo, Japan). Standardization of measurements over the years was conducted using a control serum of SRL, and the drifts of measurements were kept within an adequate level. The measurements were presented by both CAP score and U/mL. The lower limit of CAP score 1 is 0.35 U/mL (i.e. the lowest detection limit).

The diagnosis of JCPS was made from symptoms gained from the questionnaire and the serum examination. 'Definite symptoms of JCPS' had to satisfy the condition that any nasal and/or conjunctival symptom on the questionnaire that appeared in March and/or April lasted 3 weeks or longer in the surveyed year. As for 1994, the definition was different because the question above was different (i.e. the words 'in an average year' were used in 1994 instead of 'in the surveyed year'). A subject who was positive to the JCP-IgE test and had 'Definite symptoms' was diagnosed as having 'Definite JCPS'. The basis of this criterion was that JCP usually disperses from the middle of February to late March, and Japanese cypress pollen from the middle of March to early May, and symptoms lasting at least three weeks can be thought of as pollinosis.

The condition of the students' houses was also surveyed by the questionnaire. In answer to the question about passive smoking, 'Is there a smoker in the family living with the child?', the possible responses were 'Yes, currently', 'Not now, but there was in the past', or 'Never'. In answer to the question about the ventilation of the house, 'How is your house ventilated?', the possible responses were 'Well, a wooden house without aluminum-sashed windows', 'Moderately, a wooden house with aluminum-sashed windows', or 'Poorly, a concrete building'. The first type of house indicated an old traditional Japanese house, and the second indicated a modernized traditional house or recently built traditional-style house.

In answer to the question about flooring, 'What kind of flooring do you have in your house? Please choose two items for the rooms frequently used', possible responses were 'Tatami (straw mat)', 'Floor boards', 'Carpet, including that laid on tatami or other type of floor' or 'Others'. In answer to the question about heating, 'What do you use for heating? Please choose all items that you use', possible responses were 'Central heating', 'Room air-conditioner (electric)', 'Electric heater', 'Gas stove or fan heater', 'Kerosene stove', 'Kerosene fan heater', 'Charcoal or coal', or 'Others'. Kerosene stove and kerosene fan heater were differentiated because the former may produce more minute particles of soot.

Subjects and their parents were also questioned about whether they had a history of allergic disease. The question was 'Have you (your parents) been diagnosed by a doctor as having an allergic disease?' The possible responses were 'Yes', 'No' or 'Do not remember'. If 'Yes', they chose the diagnosis from a list comprising atopic dermatitis, asthma, allergic rhinitis, allergic conjunctivitis and pollinosis.

The prevalence of sensitization to JCP or HDM was defined as the proportion of children whose IgE CAP score was 1 or higher throughout the observed period. The incidence of sensitization to JCP or HDM was principally defined as the proportion who were negative to the antigen at the beginning of the observation and then changed to positive and continued to be positive during that period. The incidence was evaluated as the cumulative incidence for that period.

For statistical analysis, the Chi-squared test was used for examining the difference of distribution, while the Wilcoxon rank sum test and the Kruskal–Wallis test were used for the difference of the level. The relative risk (RR) of prevalence and cumulative incidence for the levels of JCP- and HDM-IgE and environmental factors were calculated by the method proposed by Lee[15] (using the PHREG procedure of SAS).[16]

RESULTS

The amount of dispersed pollen of Japanese cedar and Japanese cypress from February to April of each year was 165, 5941, 663 and 2007 counts in 1994, 1995, 1996 and 1997, respectively (Table 1). That of dispersed Japanese cypress was 77, 15 531, 119 and 674 counts in 1994, 1995, 1996 and 1997, respectively. Dispersion in 1994 and 1996 was small, while that in 1997 was large. Dispersion in 1995 was the largest.

The prevalence of being positive to JCP-IgE (CAP score ≥ 1) was 37, 52, 42 and 49% in 1994, 1995, 1996 and 1997, respectively. That of being highly positive (CAP score ≥ 4) was 5, 14, 10 and 17%, in 1994, 1995, 1996 and 1997, respectively. The level of JCP-IgE was significantly higher in 1995 and 1997 than in 1994 and 1996 ($P < 0.001$). The prevalence of being positive to HDM-IgE was 30, 38, 39 and 41 in 1994, 1995, 1996 and 1997, respectively. That of being highly positive was 14, 16, 16 and 17% in 1994, 1995, 1996 and 1997, respectively. The level of HDM-IgE did not differ during these 4 years ($P = 0.27$).

Table 1 shows the classification of individual longitudinal measurements of JCP-IgE with the median (U/mL) of each group. A total of 116 children (43% of the total number of subjects) had not produced JCP-IgE during those 4 years (reference group). Ten children (4%) were initially negative to JCP and even negative in the largest-dispersion year (1995), but became positive after that

(incident cases 1). The median of them was 0.61 U/mL in 1997.

Forty-one children (15%) had been initially negative to JCP but changed to positive in the largest-dispersion year (incident cases 2–5). They were classified into two major subgroups; one was those who changed to negative again in the smaller-dispersion year (incident cases 2,3), and the other was those who were persistently positive (incident cases 4,5). The former group was further divided into two groups; one was those who were still negative in the consecutive larger-dispersion year (incident cases 2), and the other was those who became positive in the same year (incident cases 3). Among the latter group, those who became negative in the consecutive larger-dispersion year (incident cases 4) were exceptional.

The median of JCP-IgE of the incident cases 2–4 was low (0.50–0.75 U/mL), although the median of the incident cases 5 was 1.50, 0.75 and 3.79 U/mL in 1995, 1996 and 1997, respectively. The IgE level of the incident cases 5 in 1996 was significantly lower than the levels in 1995 ($P = 0.023$) and 1997 ($P < 0.001$). That in 1997 was higher than that in 1995 ($P < 0.005$).

A total of 92 children (35%) were positive to JCP throughout that period (prevalent cases). The median was 3.46, 11.15, 5.42 and 12.10 U/mL in 1994, 1995, 1996 and 1997, respectively. The IgE levels in 1995 and 1997 were significantly higher than those in 1994 and 1996 ($P < 0.001$). That in 1996 was higher than that in 1994 ($P = 0.01$). Those in 1995 and 1997 did not differ ($P = 0.58$). Eight children (3%) had other patterns of sensitization, and most of them were positive at the beginning of that period and changed to negative at least once during the period. The age distribution of the children did not differ between reference children, incident cases 1–5 and prevalent cases.

Table 2 shows the relative risks of 'Definite symptoms of JCPS' for the incident cases 1–5 and prevalent cases. The prevalent cases, who were positive throughout the study, had a greater risk of having symptoms of pollinosis, although the incident cases did not. The result in 1994 was based on a different definition of the symptoms from the other years.

Table 3 shows the classification of individual longitudinal measurements of HDM-IgE with the median (U/mL) of

Table 1. Combination of longitudinal measurements of Japanese cedar pollen-immunoglobulin E, 1994–1997

Year	1994	1995	1996	1997	*n* (%)
Japanese cedar*	165	5941	663	2007	
Japanese cypress	77	15 531	119	674	
Reference group	0†	0	0	0	116 (43)
Incident cases 1**	0	0	0	0.61‡	10 (4)
Incident cases 2	0	0.50	0	0	13 (5)
Incident cases 3	0	0.53	0	0.75	10 (4)
Incident cases 4	0	0.62	0.55	0	1 (0)
Incident cases 5	0	1.50	0.75	3.79	17 (6)
Prevalent cases	3.46	11.15	5.42	12.10	92 (35)
Others	Any other combination				8 (3)
Total					267 (100)

*Counts of dispersed Japanese cedar pollen (JCP) and Japanese cypress pollen; **Incident cases 1–4 = possible incidence cases, incident cases 5 = definite incidence cases; †0 means less than 0.35 U/mL; ‡the median of IgE (U/mL).

Table 2. Relative risk (RR) and 95% confidence interval (CI) of 'Definite symptom of Japanese cedar pollinosis' for each group at different levels of the sensitization to Japanese cedar pollen-immunoglobulin E

Year	1994*		1995		1996		1997	
	RR	95% CI	RR	95% CI	RR	95% CI	RR	95% CI
Reference group	1.00		1.00		1.00		1.00	
Incident cases 1	0.85	0.39–1.84	0.95	0.43–2.06	0.82	0.38–1.79	0.84	0.31–2.32
Incident cases 2,3	0.96	0.55–1.65	0.98	0.52–1.85	1.00	0.55–1.80	0.98	0.51–1.85
Incident cases 5	1.30	0.71–2.37	1.67	0.83–3.36	1.91	0.91–3.99	1.60	0.90–2.86
Prevalent cases	1.15	0.83–1.60	1.74	1.20–2.51	1.38	0.95–2.01	1.85	1.27–2.70

*The symptoms surveyed in 1994 were the symptoms of an average year. Those surveyed in the other years were the symptoms of the surveyed year.

each group. One hundred and forty-one children (53% of the total subjects) were negative to HDM-IgE during those 4 years. The incident cases of sensitization to HDM were 33 children (12%), made up of 8, 9 and 16 children who changed to positive in 1995, 1996 and 1997, respectively. The prevalent cases were 73 children (27%). The level of IgE among the prevalent cases was apparently higher than that of the incident cases. The age distribution of the children did not differ between those three groups.

There was no difference in the level of JCP- and HDM-IgE between sexes in any of the years from 1994 to 1997. The proportion of the reference group (i.e. not sensitized children), incident cases and prevalent cases was not different between sexes for both IgE antibodies.

The association between sensitization to JCP and HDM was shown in Table 4. Among children who were sensitized to HDM at the initial survey (i.e. prevalent cases for HDM), 71% were also sensitized to JCP at the initial survey (i.e. prevalent cases for JCP), and 13% had not been sensitized to JCP during the period 1994–97 (i.e. reference group for JCP). However, 18% of the reference group for HDM were sensitized to JCP at the initial survey (i.e. prevalent cases for JCP), 18% became sensitized to JCP during the period 1995–97 (i.e. incident cases for JCP), and the remains had not been sensitized to JCP during the period 1994–97. Among those 24 incident cases for JCP among the reference cases for HDM, 21 cases became first sensitized in 1995 (the largest dispersion year).

The distribution of environmental factors assessed in 1994 varied. The number of children living with current smokers was 193 (72%), those living without smokers now but who had in the past was 30 (11%), and those who had never lived with smokers was 33 (12%). Eleven of the children did not answer. Children living in a well-, moderately or poorly ventilated house were 64 (24%), 164 (61%) and 23 (9%), respectively, with 16 not giving answers. Those living mainly with tatami, floor boards or carpets were 220 (82%), 90 (34%) and 126 (47%), respectively. Those using central heating and/or a room air-conditioner and/or an electric heater in their houses were 134 (50%). Those using a gas stove and/or a gas fan heater, a kerosene stove, or a kerosene fan heater were 21 (8%), 155 (58%) and 163 (61%), respectively. Only a small number of people used charcoal, coal or other heating.

Table 5 shows the relative risk of sensitization to JCP. The relative risk for each category of passive smoking or ventilation of the house was calculated relative to the category of 'Never' or 'Well-ventilated'. Regarding flooring and heating, the relative risk for children with a certain exposure (e.g. using tatami) was calculated relative to those without it, and then a multivariate analysis

Table 3. Combination of longitudinal measurements of house dust mite-immunoglobulin E, 1994–1997

Year	1994	1995	1996	1997	Number (%)
Reference group	0†	0	0	0	141 (53)
Incident cases	0	0	0	0.85‡	8 (3)
	0	0	0.64	1.36	9 (3)
	0	0.72	0.95	1.90	16 (6)
Prevalent cases	25.80	39.40	32.60	31.25	72 (27)
Others	Any other combination				21 (8)
Total					267 (100)

†0 means less than 0.35 U/mL; ‡the median of IgE (U/mL).

Table 4. Association of sensitization to house dust mite (HDM) and Japanese cedar pollen (JCP)

	Sensitization to JCP			
	Reference group	Incident cases	Prevalent cases	Total
Sensitization to HDM				
Reference group	89	24	24	137
Incident cases	13	11	9	33
Prevalent cases	9	11	50	70
Total	111	46	83	240

Twenty-seven cases were excluded because they were not classified into any category in the table.

was done because two or more items were chosen in the answer. The relative risks for the prevalent cases, incident cases 1,2,3 and 5 and incidence case 5 showed that neither passive smoking, the ventilation of the house nor the heating methods were associated with the sensitization to JCP.

Table 6 shows the relative risk of sensitization to HDM. No environmental condition was strongly associated with

Table 5. Relative risk (RR) and 95% confidence interval (CI) of the sensitization to Japanese cedar pollen-immunoglobulin E (JCP-IgE) for environmental factors in the house

	Prevalent cases		Incident cases1–3,5		Incident cases 5	
	RR*	95% CI	RR	95% CI	RR	95% CI
Passive smoking						
Never	1.00		1.00		1.00	
Current	0.97	0.51–1.83	0.90	0.40–2.02	0.64	0.17–2.30
In the past	1.09	0.48–2.47	0.70	0.20–2.41	0.75	0.12–4.52
Ventilation of the house						
Well	1.00		1.00		NA	
Moderate	1.45	0.85–2.49	1.39	0.68–2.84	NA	
Poor	1.22	0.48–3.10	2.11	0.83–5.36	NA	
Flooring						
Tatami	0.63	0.34–1.16	0.67	0.28–1.59	0.98	0.12–7.69
Board	1.04	0.60–1.79	1.76	0.83–3.71	1.55	0.49–4.87
Carpet	0.98	0.57–1.66	1.16	0.54–2.51	0.36	0.08–1.58
Heating						
Electric heating etc.**	0.95	0.61–1.47	1.28	0.70–2.33	1.47	0.52–4.13
Gas stove/fan heater	1.18	0.56–2.44	1.32	0.52–3.39	1.68	0.37–7.56
Kerosene stove	0.88	0.56–1.38	1.04	0.56–1.94	1.04	0.36–2.96
Kerosene fan heater	1.00	0.64–1.56	1.06	0.57–1.95	0.81	0.29–2.22

*References were those being negative to JCP-IgE during all 4 years; **central heating and/or room air-conditioner and/or electric heater; NA, not available.

Table 6. Relative risk (RR) and 95% confidence interval (CI) of the sensitization to house dust mite-immunoglobulin E (HDM-IgE) for environmental factors in the house

	Prevalent cases		Incident cases	
	RR*	95% CI	RR	95% CI
Passive smoking				
Never	1.00		1.00	
Current	0.97	0.47–1.98	1.93	0.45–8.18
In the past	1.04	0.40–2.70	2.10	0.38–11.49
Ventilation of the house				
Well	1.00		1.00	
Moderate	1.35	0.75–2.43	3.42	1.03–11.38
Poor	1.34	0.52–3.45	4.00	0.89–17.87
Flooring				
Tatami	0.74	0.36–1.53	1.67	0.43–6.55
Board	0.69	0.37–1.29	2.28	0.81–6.41
Carpet	0.76	0.43–1.33	1.28	0.44–3.75
Heating				
Electric heating etc.**	0.78	0.47–1.29	1.02	0.49–2.14
Gas stove/fan heater	1.37	0.62–3.02	1.19	0.35–4.01
Kerosene stove	1.05	0.62–1.76	3.42	1.26–9.23
Kerosene fan heater	0.98	0.59–1.64	0.95	0.46–1.97

*References were those cases who were negative to HDM-IgE during all 4 years; **central heating and/or room air-conditioner and/or electric heater.

the prevalence of sensitization to HDM. Passive smoking and flooring were not strongly associated with the incidence to it. However, children living in a poorly or moderately ventilated house had an increased risk of sensitization to HDM relative to those living in a well-ventilated house (RR = 4.00, 95% confidence interval (CI) = 0.89–17.8 for poorly ventilated; RR = 3.42, 95% CI = 1.03–11.38 for moderately ventilated). Those using kerosene stoves in their houses also had significantly increased risk relative to those not using them (RR = 3.42, 95% CI = 1.26–9.23). The relative risk for using a kerosene stove adjusted by the ventilation of the house was almost the same (RR = 3.00, 95% CI = 1.12–8.02).

Children who had a history of any allergic disease numbered 116 (43%), and those who had not numbered 95 (36%), with the remaining children answering 'did not remember' or not answering at all. Nine children had a history of asthma, 10 had urticaria, 55 had atopic dermatitis, 59 had allergic rhinitis, 28 had allergic conjunctivitis, and 14 had pollinosis. Children whose parents had a history of any allergic disease numbered 102 (38%), and children whose parents had not numbered 98 (37%). The remaining children answered 'did not remember' or did not answer at all. Seven children had parents with a history of asthma, while 16 had parents with a history of urticaria, 13 atopic dermatitis, 38 allergic rhinitis, 21 allergic conjunctivitis, and 50 pollinosis. Those who answered 'did not remember' or who did not answer were excluded from the analysis of relative risk for sensitization to JCP and HDM.

Subjects with a history of atopic dermatitis had a high risk of prevalence of sensitization to JCP (RR = 2.23, 95% CI = 1.42–3.50), incidence 1–3, 5 (RR = 2.21, 95% CI = 1.13–4.33) and incidence 5 of sensitization to JCP (RR = 2.99, 95% CI = 0.92–9.35). They also had a high risk of prevalence of sensitization to HDM (RR = 2.80, 95% CI = 1.65–4.65) and incidence of sensitization to HDM (RR = 3.00, 95% CI = 1.32–6.78). Those with a history of allergic rhinitis had a high risk of prevalence of sensitization to JCP (RR = 1.71, 95% CI = 1.08–2.70), incidence 5 of sensitization to JCP (RR = 2.82, 95% CI = 0.97–8.13) and prevalence of sensitization to HDM (RR = 2.59, 95%CI = 1.56–4.30). History of other allergic disease showed a point estimate of relative risk more than 1.0, but they were not significant at all.

Parents' history of allergic disease mostly showed a point estimate of relative risk more than 1.0 for sensitization to JCP and HDM. History of allergic conjunctivitis, only, increased at the risk of incident cases of sensitization to HDM (RR = 2.59, 95% CI = 1.04–6.45).

DISCUSSION

The purpose of this study was to clarify how children become sensitized to a specific antigen. The sensitization is regulated by individual susceptibility, exposure to the antigen, and environmental factors. Individual susceptibility is determined by genetic disposition and other characteristics such as age, history of infections, environmental factors, psychological disposition etc. Some of the environmental factors modify the strength of the exposure to the antigen; for example, a modern and poorly ventilated house is warm in winter and more humid in all seasons, which increases the amount of house dust mites. The others act as 'adjuvants'.[1]

If a defined population is equally exposed to the antigen, the level of the antigen-specific IgE mostly represents individual susceptibility. In the largest-dispersion year, 1995, more than half of the subjects were positive to JCP, but some of them changed to negative in the following year when there was less pollen. The JCP-IgE levels of the prevalent cases and incident cases 5 varied with the amount of dispersed pollen, although the level among the incident cases 5 was far lower than that among the prevalent cases. The levels among the incident cases 1–3 also seemed to correspond to the amount of dispersed pollen because the level was so low that the IgE was not detected in years with low pollen counts. The reference children did not produce JCP-IgE at a detectable level during these 4 years, but they might have produced the IgE if they had been more strongly exposed to JCP, or the IgE might have been detected if the measurement had been more sensitive. These findings show that there is a wide variety of susceptibility to the antigen. Consequently, cases cannot be dichotomously divided into those 'sensitive to the antigen' and those 'not sensitive to the antigen'.

The prevalent cases had a significantly higher potential for producing the symptoms of JCPS than the reference children, but the incident cases 1–3 did not. The incident cases 5 may have had as high a potential as the prevalent cases, although this is uncertain because of the small number of subjects. This fact is consistent with the difference of the JCP-IgE levels of those groups. Therefore, it can be said that the prevalent cases and incident cases 5 are clinically significantly sensitized to JCP. This statement can be made because the sensitization to JCP is strongly related to the symptoms of JCPS.

The incident cases 5 were undoubtedly thought to be incident cases of sensitization to JCP because they first

changed to positive to JCP in 1995 and then continued to be positive. This is also strongly suggested by the fact that the JCP-IgE level of the group had become higher in 1997 than it was in 1995, whereas the levels of both prevalent cases and incident cases 3 did not differ between those two years. However, it is not certain whether the JCP-IgE level of the incident cases 5 could reach the level of the prevalent cases. The incident cases 1–3 were thought to be possible incident cases because they once changed to positive to JCP, but it is less plausible considering their low JCP-IgE levels and also considering the previous discussion about the relationship to the symptoms.

Therefore, it is suggested that sensitization to JCP among children with strong susceptibility was mostly completed before their enrollment in this study. Some further children can be sensitized at any age between 6 and 14 years if they are exposed to an extraordinary amount of JCP (6%, incident cases 5). Some of the remaining children could also temporarily produce quite low levels of JCP-IgE following strong exposure to the antigen (13%, incident cases 1–3).

House dust mite is an indoor antigen in a house. The exposure to HDM differs from person to person depending on the conditions of each house, although these conditions are relatively stable. Sensitization to HDM among the children with strong susceptibility was also mostly completed before their enrollment in this study (prevalent cases, 27%). Some further children became sensitized at any age between 6 and 14 years (incident cases, 12%). Their level of HDM-IgE was apparently lower than that of the prevalent cases, and it is uncertain whether the level could increase to the same level as that of the prevalent cases.

The IgE levels of the prevalent cases of sensitization to both JCP and HDM were higher than those of the incident cases. These prevalent cases were not associated with any environmental factor surveyed. The risk factors may have been avoided because the subjects were already aware of their sensitization, but their serum IgE would only have been examined if they had visited clinics for allergic symptoms or other reasons. This bias, therefore, may be smaller than the bias among people with symptoms who have already avoided risk factors because of their symptoms. It is more likely that the prevalent cases were of such strong susceptibility to the antigen that they had been sensitized to it before the enrollment in this study regardless of the environmental factors.

The incidence of sensitization to JCP was not associated with any of the environmental factors. The changing of cases to positive to JCP-IgE seemed mostly to depend on the exposure to the large amount of the dispersed pollen. As for HDM, the ventilation of houses and using a kerosene stove increased the risk of the incidence. These facts suggested that the children with weak susceptibility could have been sensitized to the antigens under some circumstances such as an extraordinary exposure to the antigen or exposure to some environmental factors.

The ventilation of houses is one of the most important factors for sensitization to HDM.[1] A poorly ventilated house is rather warm and humid, and the amount of HDM increases in those circumstances. In this study, both poorly and moderately ventilated houses showed an increased risk for sensitization to HDM relative to the well-ventilated house. The reason why only the latter was significant is thought to be the small number of the subjects living in a poorly ventilated house. It was reported that both HDM- and JCP-IgE levels were higher among the children living in a house made of concrete than in a wooden house in a cross-sectional study.[13] It was also reported that the HDM-IgE level was higher among those having carpets in the house than among those having other flooring, although JCP-IgE level was not.[10,14] The results of this study are substantially consistent with those previous results, but in this study the sensitization to JCP was not affected by the condition of the house. It seemed more reasonable than the previous results because JCP is an outdoor allergen and the school children spend long periods of time outside their houses, where they can be sensitized.

Having carpets in the house is thought to increase the amount of HDM.[1] In this study, flooring which consisted of boards showed rather high, but not significant, relative risks of sensitization to both JCP and HDM. Exposure to HDM is determined by other interior conditions (i.e. bedding, the cleaning of rooms) than the conditions surveyed in this study. Therefore, these results may be affected by those unexamined factors or be chance findings.

Using a kerosene stove increased the risk of the incidence of sensitization to HDM in this study, although both a gas stove/fan heater and a kerosene fan heater did not. It was reported that both kerosene and gas heating increased the level of NO_2 in the indoor environment,[17,18] but only kerosene heating increased the level of SO_2.[18] The level of suspended particulated matter (SPM), benzo[a]pyrene and benzo[ghi]perylene were increased by using a conventional or reflection kerosene stove, but were not increased by using a kerosene fan heater.[18] It is still controversial whether air pollution increases the level of IgE and the risk of asthma and hay fever,[1] and whether it is related to JCPS.[8,9]

In addition to the gas components of air pollutants, it was reported that the sensitization to ovalbumin or the

major allergen of JCP was enhanced by the coexistence of diesel-exhaust particles *in vivo* through an intraperitoneal or intranasal route in mice.[19,20] In humans, it was reported that aromatic hydrocarbons from diesel exhaust had a direct effect on B-cells, leading to enhanced IgE production *in vitro*.[21] These results may be applied to HDM combined with oil-soot particles from a kerosene stove. On the contrary, JCP is hard to combine with particles from a kerosene stove because it is an outdoor antigen, so it is consistent that a kerosene stove as well as the other heating methods did not increase the risk of sensitization to JCP.

Smoking and passive smoking are generally recognized as enhancing the sensitization to allergens.[1] A longitudinal observation for 4 years showed that parental smoking enhanced allergic sensitization.[4] However, some cross-sectional studies showed that smoking or passive smoking decreased the risk of sensitization to outdoor antigens such as grass[22,23] or JCP,[10] although it did not decrease and may have increased the risk of sensitization to HDM.[22,23] So-called 'healthy smokers' bias' cannot completely explain this inconsistency.[22] In this study, passive smoking showed no association with either prevalence or incidence of sensitization to JCP or HDM. The children who had never been exposed to passive smoking (the reference group) were small in number. The severity of passive smoking at home was not surveyed in this study. These conditions seemed to make the analysis difficult.

It was shown that passive smoking somewhat increased the risk of the incidence of sensitization to HDM and decreased the risk of it to JCP, whereas the relative risks for the prevalence of them were nearly equal to one. If these relative risks of the incidence are significant, the following hypothesis could be supported. Although smoking is generally thought to enhance allergic sensitization, the enhancement might be due to increased permeability of bronchial mucosa for allergens by local inflammation or enhanced immunologic recognition on bronchial mucosa by allergen combined with smoke. Alternatively, the immunologic effect of smoking could be suppressive to allergic sensitization. Indoor allergens such as HDM could be easily combined with the suspended particles in the smoke and the sensitization to HDM could be enhanced. However, outdoor allergens such as grass or JCP are hard to combine with the suspended particles of smoke and thus, sensitization to them could be suppressed.

Allergic sensitization is thought to be associated with allergic diseases or atopic disposition. History of atopic dermatitis was strongly associated with both prevalence and incidence of sensitization to JCP and HDM in this study. Atopic dermatitis emerges earliest in the 'atopic march', so it is most likely diagnosed before the age of the subjects in our study.[1] Other allergic diseases such as asthma may emerge after this age. History of allergic rhinitis was associated with sensitization to HDM rather than with JCP, probably because this diagnosis is more likely used for perennial allergic rhinitis. Allergic conjunctivitis and pollinosis were not associated with sensitization to JCP or HDM because these are more likely to be diagnosed after this age (children with a history of these diseases were rather less; 28 and 14, respectively) or these diagnoses may be clinically given by a doctor without allergic examination. Parents' history of allergic diseases was not clearly associated with sensitization to JCP or HDM among their children. It may be because the parents' history did not well represent allergic disposition, and those diagnoses and recall of them were ambiguous.

Conclusion

The susceptibility to an antigen varies continuously, so it is difficult for the subjects to be divided dichotomously between 'sensitive to the antigen' or 'not sensitive to the antigen' by the IgE level itself. Three levels of susceptibility can be roughly assumed by considering other factors. First, children who had been already sensitized before their enrollment in this study and who were still positive during the ages of 6–14 years (prevalent cases) were of such strong susceptibility to the antigen that they could be sensitized regardless of the environmental factors in this study. However, the susceptibility could be related to the environment if the prevalent cases were studied when they were sensitized. They were at a high level of IgE and exhibited strong antigen-specific symptoms. Those with weak susceptibility could be sensitized during that age by an extraordinary exposure to the antigen (e.g. JCP) or by the effect of the environmental risk factors (e.g. the ventilation of the house and the use of a kerosene stove in the case of HDM). They were at a low level of IgE and exhibited weak antigen-specific symptoms. The rest were never sensitized.

Acknowledgements

We would like to thank Professor P. Burney of the Department of Public Health Medicine, the United Medical and Dental School of Guy's and St Thomas's Hospitals, for his critical reading of the manuscript. We

would also like to thank the school doctors Dr K. Ochi and Dr M. Yanagisawa, the nursing teachers of the primary and junior high schools in the town, the chief pharmacist and technician of the town clinic Mr J. Kubo, and the technicians and nurses in the town for their help with the surveys and the measurement of dispersing pollen. We thank Dr N. Takagi and Dr T. Hama of the Department of Otorhinopharyngolaryngology, Kyoto Prefectural University of Medicine for the measurement of dispersing pollen. The Education Board of the town and the school principals are also thanked for giving permission to conduct the surveys.

This study was supported in part by a Grant-in-aid for Scientific Research (C) (No. 08670448) from the Ministry of Education, Science, Culture, and Sport of Japan.

REFERENCES

1 Björkstén B. Risk factors for sensitization and development of allergic diaseases. In: Blumental MN, Björkstén B (eds). *Genetics of Allergy and Asthma*. New York: Dekker, 1997; 171–195.
2 Gassner M. Immunologic reactions and allergies in altered environmental conditions (in German with English abstract). *Schweiz Rundshc. Med. Prax.* 1992; 81: 426–30.
3 Nakagomi T, Itaya H, Tominaga T, Yamaki M, Hisamatsu S, Nakagomi O. Is atopy increasing? *Lancet* 1994; 343: 121–2.
4 Ronchetti R, Bonci E, Cutrera R *et al.* Enhanced allergic sensitization related to parental smoking. *Arch. Dis. Child* 1992; 67: 496–500.
5 Horiguchi S, Saito Y. Japanese cedar pollinosis in Nikko, Japan (in Japanese with English abstract). *Arerugi [Jpn. J. Allergol.]* 1964; 13: 16–8.
6 Mori A. Sensitization and onset of Japanese cedar pollinosis in children (in Japanese). *Arerugi [Jpn. J. Allergol.]* 1995; 44: 7–15.
7 Ishizaki T, Koizumi K, Ikemori R, Ishiyama Y, Kushibiki E. Studies of prevalence of Japanese cedar pollinosis among the residents in a densely cultivated area. *Ann. Allergy* 1987; 58: 265–70.
8 Takagi M. Environmental and immunological survey of sensitization with Japanese cedar pollen in children (in Japanese with English abstract). *Arerugi [Jpn. J. Allergol.]* 1988; 37: 1065–71.
9 Inoue S, Sakaguchi M, Morita M *et al.* Regional difference in the prevalence of IgE antibody to Japanese cedar pollen allergens (in Japanese with English abstract). *Igaku No Ayumi* 1988; 145: 121–2.
10 Osaka F, Kasuga H, Sugita M, Matsuki H, Miyake T. A study on the relationship between Japanese cedar IgE in the serum of school children and the housing environment (in Japanese with English abstract). *Arerugi [Jpn. J. Allergol.]* 1987; 36: 72–80.
11 Ozasa K, Takenaka H, Takagi N, Aoike A, Kawai K. A case control study of risk factors for Japanese cedar pollinosis (in Japanese with English abstract). *Nihon Eiseigaku Zasshi [Jpn. J. Hygiene]* 1995; 50: 622–30.
12 Ozasa K, Takenaka H, Takagi N, Aoike A, Kawai K. A cross-sectional study of factors associated with production of Japanese cedar pollen specific IgE antibody and total IgE antibody, and symptoms of Japanese cedar pollinosis in primary school children (in Japanese with English abstract). *Arerugi [Jpn. J. Allergol.]* 1995; 44: 1361–8.
13 Osaka F, Kasuga H, Sugita M, Matsuki H, Miyake T. A study on the relationship between mite IgE in the serum and the housing environment in school children (Part 1) (in Japanese with English abstract). *Nihon Koshueisei Zasshi [Jpn. J. Public Health]* 1985; 32: 731–7.
14 Osaka F, Kasuga H, Sugita M, Matsuki H, Miyake T. A study on the relationship between mite IgE in the serum and the housing environment in school children (Part 2) (in Japanese with English abstract). *Nihon Koshueisei Zasshi [Jpn. J. Public Health]* 1986; 33: 3–10.
15 Lee J. Odds ratio or relative risk for cross-sectional data? *Int. J. Epidemiol.* 1994; 23: 201–3.
16 SAS/STAT Software. The PHREG procedure. SAS, Technical Report P-, 217. Cary NCSAS, Institute 1991, 1.
17 Leadrer BP, Zagraniski RT, Berwick M, Stolwijk JAJ. Assessment of exposure to indoor air contaminants from combustion sources: methodology and application. *Am. J. Epidemiol.* 1986; 124: 275–89.
18 Arashidani K, Yoshikawa M, Kawamoto T, Matsuno K, Kayama F, Kodama Y. Indoor pollution from heating. *Industrial Health* 1996; 34: 205–15.
19 Muranaka M, Suzuki S, Koizumi K, Takafuji S, Miyamoto T. Adjuvant activity of diesel-exhaust particulates for the production of IgE antibody in mice. *J. Allergy Clin. Immunol.* 1986; 77: 616–23.
20 Takafuji S, Suzuki S, Koizumi K, Tadokoro K, Miyamoto T. Diesel-exhaust particulates inoculated by the intranasal route have an adjuvant activity for IgE production in mice. *J. Allergy Clin. Immunol.* 1987; 79: 639–45.
21 Takenaka H, Zhang K, Diaz-Sanchez D, Tsien A, Saxon A. Enhanced human IgE production results from exposure to the aromatic hydrocarbons from diesel exhaust: direct effects on B-cell IgE production. *J. Allergy Clin. Immunol.* 1995; 95: 103–15.
22 Jarvis D, Luczynska S, Chinn S, Burney P. The association of age, gender and smoking with total IgE and specific IgE. *Clin. Exp. Allergy* 1995; 25: 1083–91.
23 Arshad SH, Hide DW. Effect of environmental factors on the development of allergic disorders in infancy. *J. Allergy Clin. Immunol.* 1992; 90: 235–41.